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SCHEINER, L

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on MAY 14, 1990 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-21 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-21 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The finality of the last Office action of 2/9/90, paper no. 9, has been withdrawn.

Orgel and Wallace, although not relied upon are cited as of interest. Whiteley et al and Mullis et al, although previously cited are newly applied.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-21 are rejected under 35 U.S.C. 103 as being unpatentable over Mullis, et al, in view of Carr and Whiteley, et al.

Mullis shows a method of amplifying a contiguous fragment of nucleic acid involving creating a single stranded nucleic acid (SS DNA); creating a complementary strand; denaturing the newly formed complementary strand from the old nucleic acid sequence; repeating the process whereby now the old single stranded DNA and the newly formed complementary strand are used as the SS DNA and are used to form a new set of duplexes. This process occurs one or more times and Mullis, et al, point out the great value of repeating the process a large number of times since it results in a geometric amplification of the duplex. Mullis, et al, forms the complementary strand using a polymerase enzyme while

applicants form the complementary strand by ligating fragments together; however, one of ordinary skill in the art would know that a complementary strand could be formed by ligating smaller fragments together. Carr and et al. TEACH THAT A COMPLEMENTARY STRAND
Whitely, can be formed by ligating fragments together either with a ligase (Carr and Whitely et al.) or by use of a polymerase (CARR). ONE OF ORDINARY SKILL IN THE art would know that what was important was the formation of the complementary sequence and that whether one used short fragments (amplification probes) or DNA and a polymerase or short fragments of DNA and a ligase with or without a polymerase that the only thing of importance was the formation of a complementary strand which could be used in subsequent reactions. Examiner notes that the phosphate ester linkage, catalyzed by ligase occurs by chemically reacting a hydroxyl group with a phosphate group. Thus the invention as claimed would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-21 are rejected under 35 U.S.C. 103 as being unpatentable over Carr and Whiteley et al. in view of Mullis et al.

Carr and Whiteley et al. teach an assay method which entails: Utilizing as an initial template and hybridizing two fragments to it. Ligating those fragments together and denaturing the fragments. they do not iterate the process to obtain an amplification

and they do not use both strands of the initial template. Mullis et al. teaches the importance and value of using both strands and an iterative procedure in order to amplify the target sequence. The method of modification to the primary references to obtain an amplification would be obvious in light of the teachings of Mullis et al. Thus the invention as claimed would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to a plurality of denatured pairs of amplification probes. See MPEP 706.03(n) and 706.03(z)

The specification is not enabling for hybridized pairs of amplification probes because said probes would be unable to hybridize to amplification sequence.

Claims 2, 3, 10, 11, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to a thermostable ligase. See MPEP 706.03(n) and 706.03(z).

Only one enzyme is disclosed and it would require one of ordinary skill in the art an undue amount of experimentation to find enzymes other than a thermostable ligase that would function in the instant assay; therefor the scope of the claim should be narrowed.

Claim 19 is rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"Sufficiently adjacent" fails to particularly point out and distinctly claim the subject matter which applicants regard as the invention because the limitation of the specification must be read into the claims and the specification is enabling for a one nucleotide gap only wherein ligation is concerned as no fill-in reactions are disclosed. That is if more than one nucleotide was required to fill the gap between adjacent amplification probes for purposes of achieving the amplification product a Klenow fragment of DNA polymerase 1 or other similar enzyme would have to be employed and no such system is disclosed. --Amplification probes binding to template sequence (Amplification sequence) in a contiguous manner having a gap of no more than one nucleotide between said probe sequences-- might be acceptable language. (In re Windhaus, et al. 188 USPQ 129; In re Lundberg, et al. 113 USPQ 530).

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to a target nucleic acid sequence wherein the nucleotide sequence is known. See MPEP 706.03(n) and 706.03(z).

Claims 1-21 are not enabled for "a target nucleic acidsequence" or "Amplification sequence" because one would not know what synthetic oligonucleotide sequence (amplification probes) to generate and it would be critical that the probes were 100% homologous to template in order to maintain the integrity of sequence following repeated cycling.

Claims 1-21 are rejected under 35 U.S.C. 112 first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Functional language should be recited in claims regarding probe length as the limitations of the specification must be read into the claims. However the specification does not teach probe length and is therefor not enabling for a plurality of denatured pairs of amplification probes. Because probe number and respective lengths are critical to the hybridization reaction as it is both individual probe length and excess concentration of probe that will "drive the reaction foward".

Claims 6, 7, 9, 14 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6, 7, 9, 14 and 21 are vague and indefinite in their recitation of "a different combination of amplification probe segments".

Any inquiry concerning this communication should be directed to Laurie Scheiner at telephone number 703-557-3506.

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SCHEINER ew
06-18-90

Sam Rosen
SAM ROSEN
EXAMINER